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EXAMINER	
MACAULEY, SHERIDAN R	
ART UNIT	PAPER NUMBER
1651	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,296	MARRERO MIRAGAYA ET AL.	
	Examiner	Art Unit	
	SHERIDAN R. MACAULEY	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-28 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-28 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/21/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A response and amendment were received and entered on January 21, 2009. All evidence and arguments have been fully considered. Claim 1-25 and 29-32 are cancelled. New claims 34-35 have been added. Claims 26-28 and 33-35 are pending and examined on the merits in this office action.

Claim Rejections - 35 USC § 112

1. Rejections under 35 USC 112 have been withdrawn due to amendment.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 26-28 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Eschenfelder et al. (US 4,944,943, cited in prior action) in view of Baldwin (US 5,098,707, cited in prior action). The claims recite a method for treating hemorrhoid disease in a human in need thereof, comprising administering to said human an effective amount of a pharmaceutical composition, said composition consisting essentially of a thrombolytic protein selected from the group consisting of tissue-type plasminogen activator (t-PA), urokinase (u-PA), streptokinase (SK), or a combination thereof, wherein the pharmaceutical composition is administered rectally. Further claimed embodiments include that the pharmaceutical composition consists essentially of recombinant SK and a carrier or excipient, wherein the concentration of SK is 50,000 to 1,500,000 IU per gram of pharmaceutical composition, and that the composition is administered as a suppository.

6. Baldwin teaches compositions comprising streptokinase for the treatment of vascular disease (abstract; col. 1, lines 34-46, col. 24, lines 1-35). Baldwin teaches that these compositions may be formulated in rectal compositions, such as suppositories, containing a carrier that is pharmacologically acceptable for rectal administration (col.

24, lines 32-35). Baldwin teaches that the streptokinase that is used in the composition may be of recombinant origin (col. 4, lines 8-17). Baldwin teaches that 1,500,000 units of streptokinase may be used in the composition (col. 24, lines 13-19). The reference does not disclose the use of the composition for the treatment of hemorrhoid disease.

7. Eschenfelder teaches a method for the treatment of vascular disorders, such as hemorrhoid disease, comprising administering a thrombolytic substance such as streptokinase, to a patient in combination with an antithrombotic substance (col. 1, lines 26-36, col. 2, lines 21-41). Eschenfelder teaches that it was known at the time of the art to treat such disorders with thrombolytic substance in the absence of an antithrombotic (col. 1, lines 9-12, col. 2, lines 30-32).

8. At the time of the invention, a method of treating vascular using a composition comprising streptokinase was known, as taught by Baldwin. It was further known that streptokinase-containing compositions could be used for the treatment of hemorrhoid diseases and could be administered using the claimed conditions (i.e., as a suppository). One of ordinary skill in the art would have been motivated to combine these teachings because Eschenfelder teaches that streptokinase-containing compositions could be used for the treatment of hemorrhoid diseases and Baldwin teaches methods of preparing such compositions (col. 2, lines 21-41). Although Eschenfelder teaches the improvement of a composition comprising a thrombolytic substance by the addition of an antithrombotic agent to such compositions, it is clear from the teachings of Eschenfelder that the use of an antithrombotic such as streptokinase for the treatment of a vascular disease such as hemorrhoid disease was

known at the time of the invention. One of ordinary skill in the art would therefore have understood that an antithrombotic agent could have been formulated as described by Baldwin in the absence of any additional active components for use in a method of treating hemorrhoid disease. Further, one of ordinary skill in the art would have recognized that the amount taught by Baldwin could be used and varied over the course of routine experimentation to arrive at a composition with the claimed amount of streptokinase. One of ordinary skill in the art would have had a reasonable expectation of success in combining these teachings because both teach the manufacture of a composition comprising streptokinase that is suitable for use with multiple carriers. It would therefore have been obvious to one of ordinary skill in the art to combine the teachings discussed above to arrive at the claimed invention.

9. Claims 26-28 and 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eschenfelder et al. (US 4,944,943) in view of Baldwin (US 5,098,707, cited in prior action) as applied to claims 26-28 and 33 above, and further in view of Ivy (US 5.720,962) and Oh (WO 01/22935 A1). Claims 26-28 and 33 are discussed above. Claims 34 and 35 recite a method for treating hemorrhoid disease in a human in need thereof, comprising administering to said human an effective amount of a pharmaceutical composition, said composition consisting essentially of a thrombolytic protein selected from the group consisting of tissue-type plasminogen activator (t-PA), urokinase (u-PA), streptokinase (SK), or a combination thereof, EDTA, and sodium

diclofenac, or sodium salicylate., wherein the pharmaceutical composition is administered rectally.

10. Baldwin teaches compositions comprising streptokinase for the treatment of vascular disease (abstract; col. 1, lines 34-46, col. 24, lines 1-35). Baldwin teaches that these compositions may be formulated in rectal compositions, such as suppositories, containing a carrier that is pharmacologically acceptable for rectal administration (col. 24, lines 32-35). Baldwin teaches that the streptokinase that is used in the composition may be of recombinant origin (col. 4, lines 8-17). Baldwin teaches that 1,500,000 units of streptokinase may be used in the composition (col. 24, lines 13-19).

11. Eschenfelder teaches a method for the treatment of vascular disorders, such as hemorrhoid disease, comprising administering a thrombolytic substance such as streptokinase, to a patient in combination with an antithrombotic substance (col. 1, lines 26-36, col. 2, lines 21-41). Eschenfelder teaches that it was known at the time of the art to treat such disorders with thrombolytic substance in the absence of an antithrombotic (col. 1, lines 9-12, col. 2, lines 30-32).

12. As discussed above, it would have been obvious to combine the teachings of Baldwin and Eschenfelder to arrive at nearly all of the elements of the claimed invention. Neither of the reference, however, teaches a composition comprising EDTA, sodium diclofenac, or sodium salicylate.

13. Ivy and Oh both teach compositions for the treatment of hemorrhoid disease. Ivy teaches compositions comprising EDTA (abstract, col. 2, lines 21-25) and Oh teaches compositions comprising salicylic acid and diclofenac (p. 5, lines 26-35, p. 3, lines 5-25).

14. For the reasons discussed above, a method of treating hemorrhoid disease comprising nearly all of the claimed elements would have been obvious at the time of the invention, as taught by Eschenfelder and Baldwin. It was also known at the time of the invention that EDTA, salicylic acid, and diclofenac were pharmaceutically acceptable additives to compositions for the treatment of hemorrhoid disease. One of ordinary skill in the art would have been motivated to add these components for a composition for carrying out the claimed method because Baldwin teaches that the compositions may contain other pharmaceutically accepted ingredients (col. 24, lines 20-41). There existed at the time of the invention a finite number of predictable potential additives to a composition for use in a method of treating hemorrhoid disease, including the additives taught by Ivy and Oh. One could have used these additives with a reasonable expectation of success because all of the references teach that the compositions were suitable for use in a method for the treatment of hemorrhoid disease. It would therefore have been obvious to combine the teachings discussed above to arrive at the claimed method.

15. Thus, the claimed invention as a whole was *prima facie* obvious over the combined teachings of the prior art.

Response to Arguments

16. Applicant's arguments filed January 21, 2009 have been fully considered but they are not persuasive. Applicant argues that the claims are not obvious in view of the cited

references because the claims fail to render obvious a method comprising the administration of a composition consisting essentially of a thrombolytic protein. Applicant argues that one of ordinary skill in the art would not have a reasonable expectation of success in combining the teachings of the prior art to arrive at the claimed invention. Applicant argues that, at the time of the invention, the prior art taught away from the administration of a thrombolytic protein, as recited in the method of the claims. Applicant also argues that the references do not render the claimed invention obvious because the Oh reference does not teach a composition for rectal administration.

17. In response to applicant's argument that that the claims are not obvious in view of the cited references because the claims fail to render obvious a method comprising the administration of a composition consisting essentially of a thrombolytic protein, it is noted that Eschenfelder teaches that it was known at the time of the art to treat such disorders with thrombolytic substance in the absence of an antithrombotic, as discussed above. Although Eschenfelder teaches the improvement of a composition comprising a thrombolytic substance by the addition of an antithrombotic agent to such compositions, it is clear from the teachings of Eschenfelder that the use of an antithrombotic such as streptokinase for the treatment of a vascular disease such as hemorrhoid disease was known at the time of the invention. One of ordinary skill in the art would therefore have understood that an antithrombotic agent could have been formulated as described by Baldwin in the absence of any additional active components for use in a method of treating hemorrhoid disease. Although applicant argues that Baldwin also does not

teach a composition consisting essentially of streptokinase, it is noted that, regardless of the presence of additional components in the composition of Baldwin, compositions comprising only a thrombolytic protein were known in the art at the time of the invention, as taught by Eschenfelder and discussed above. Therefore, the combination recited in the claims would have been obvious in view of the combined teachings of the prior art.

18. Regarding applicant's argument that one of ordinary skill in the art would not have a reasonable expectation of success in combining the teachings of the prior art to arrive at the claimed invention, it is noted that the claims recite "a method of treating a patient." The administration of a composition containing a thrombolytic protein by the rectal route as recited in the claims was known in the art at the time of the invention, as discussed in the rejections above. One of ordinary skill in the art would therefore have had a reasonable expectation of success in performing said treating by administering the composition recited in the claims, regardless of whether one would expect the composition to possess activity. Applicant's argument is therefore not found to be persuasive.

19. Regarding applicant's argument that, at the time of the invention, the prior art taught away from the administration of a thrombolytic protein, as recited in the method of the claims, it is noted that the prior art cited in this office action is directed to the administration of a thrombolytic protein by the rectal route. Although applicant argues that none of the references teach that a composition consisting essentially of such a protein can be administered, this is taught by the Eschenfelder reference, as discussed above. Although applicant cites Bachmann as "teaching away" from the claimed

invention, it is noted that the reference does not discuss any detrimental effects to the rectal administration of a thrombolytic protein and only discusses the minimal thrombolytic activity resulting from such an administration. Applicant's further arguments regarding the teaching of Yamamoto and Nisar do not provide any additional evidence of the teaching away of the prior art from such a composition. Although Yamamoto teaches that the formulation of peptides into compositions for rectal administration is difficult, thrombolytic proteins were known to be formulated into rectal compositions at the time of the invention, as taught by Eschenfelder and Baldwin. Furthermore, the absence of a formulation consisting essentially of a thrombolytic protein in the Nisar review does not provide evidence of its being unknown in the art; such compositions were known in the art at the time of the invention, as taught by Eschenfelder. Therefore, the prior art at the time of the invention has not been found to teach away from the claimed invention.

20. In response to applicant's argument that the references do not render the claimed invention obvious because the Oh reference does not teach a composition for rectal administration, it is noted that the reference teaches that the administration of common anti-inflammatory compositions to localized regions was known. Although Oh teaches the administration of the compositions by another route, one of ordinary skill in the art would have recognized that such compositions may be administered in another common formulation, such as a formulation for rectal administration.

21. Therefore, applicant's arguments have been fully considered, but they have not been found to be persuasive.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHERIDAN R. MACAULEY whose telephone number is (571)270-3056. The examiner can normally be reached on Mon-Thurs, 7:30AM-5:00PM EST, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (571) 272-0926. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SRM

/Ruth A. Davis/
Primary Examiner, Art Unit 1651